Improved Treatment and Survival for Lung Cancer Patients in South-East Scotland

Sara C. Erridge, MD, MBBS, FRCP (Edin), FRCR,† Brian Murray, MSc,‡ Allan Price, PhD, MB, ChB, FRCP (Edin), FRCR,*† Janet Ironside, MB, ChB, FRCR,* Felicity Little, MBBS, MRCP (UK), FRCR,* Melanie Mackean, MD, MB, ChB, MCRP (UK),*† William Walker, MB, BChir, BA, FRCS,†§ David H. Brewster, MD, MSc, MB, ChB, FFPH, MRCGP,†‡ Roger Black, MA,‡ and Ron J. Fergusson, MD, MB, ChB, FRCP (Edin),|| on behalf of South-East Scotland Cancer Network Lung Cancer Team*

Introduction: Lung cancer survival in Scotland has historically been poor but many changes to the lung cancer services have been introduced and this study was conducted to investigate the impact of these changes on treatment and survival.

Methods: Data obtained from the Scottish Cancer Registry, South-East Scotland Cancer Network audit and Edinburgh Cancer Centre database were used to conduct a comparison of the management and outcomes of lung cancer patients from South-East Scotland diagnosed in 1995 and in 2002.

Results: Data on 971 patients diagnosed in 2002 and 927 in 1995 were analyzed and demonstrated that though the use of treatment overall had not changed (62% in 2002 versus 63% in 1995) the use of potentially curative radiotherapy (15 versus 5% χ^2 $p < 0.001$) and chemotherapy for non-small cell lung cancer (18 versus 7% χ^2 $p < 0.001$) had increased, but not resection rates (11 versus 10%). The use of palliative radiotherapy declined (38% versus 31% χ^2 $p < 0.001$). Patients diagnosed in 2002 had an adjusted hazard of death of 0.7 (95% confidence interval, 0.6–0.8) compared with 1995, with median survival from date of diagnosis of 5.2 versus 4.1 month and 2 year overall survival 15 versus 11% (log rank $p = 0.004$). Localized disease and younger age were also associated with a reduced hazard of death.

Conclusions: Patients diagnosed with lung cancer in Scotland in 2002 had a reduced hazard of death and improved survival compared with 1995. It is hypothesized that this was due in part to improvements in service organization and increased use of treatments likely to increase survival.

Key Words: Lung cancer, Treatment, Population-based, Survival.

(*J Thorac Oncol.* 2008;3: 491–498)

Although there have been sizeable improvements in the outcome of patients with many cancers,[1] population-based survival after a diagnosis of lung cancer has changed little over the last 20 years, and remains unacceptably low.[1–3]

The results of a Scottish national audit of lung cancer patients diagnosed in 1995 have been previously published,[4–6] and demonstrated poor outcome with a median survival of 3.6 months for all Scottish patients. Since 1995, there have been a number of changes to healthcare organization and the staff treating lung cancer in South-East Scotland, which have included:

1. The introduction of a managed clinical network (South-East Scotland Cancer Network or SCAN) to ensure smoother referral pathways and better patient management.
2. The introduction of national patient management guidelines through the Scottish Intercollegiate Guidelines Network. The first lung cancer guidelines were published in 1998 and revised in 2005.
3. The introduction of multidisciplinary team meetings at which all newly diagnosed patients are discussed.
4. Appointment of more oncologists specializing in lung cancer; the number increased from 2 in 1995 to 4 in 2002. Consequently, all patients should have the opportunity to benefit from the opinion of a specialist respiratory oncologist.

Other changes in clinical practice have also occurred, primarily:

1. Greater access to computed tomography (CT) scanning and the development of scanners with improved image quality.

*Edinburgh Cancer Centre, Western General Hospital, Edinburgh; †University of Edinburgh, Western General Hospital, Edinburgh; ‡Information and Statistics Division, NHS Scotland; §Department of Cardiothoracic Surgery, New Royal Infirmary, Little France, Edinburgh; ||Department of Respiratory Medicine, Western General Hospital, Edinburgh.

Disclosure: The authors declare no conflict of interest.

Sources of finance: No specific sources of funding for this project though Dr Sara Erridge was funded by Edinburgh Cancer Centre Endowment Fund. This work formed part of a Doctorate of Medicine thesis awarded to Dr Sara Erridge by the University of London in 2007.

Address for correspondence: Sara C. Erridge, MD, MBBS, FRCP, Edin, FRCR, Edinburgh Cancer Centre, University of Edinburgh, Western General Hospital, Edinburgh, EH4 2XU. E-mail: serridge@staffmail.ed.ac.uk

ISSN: 1556-0864/08/0305-0491

2. Increasing evidence supporting the use of chemotherapy in stage III and IV non-small cell lung cancer (NSCLC).
3. Increasing evidence on the use of chemo-radiation in limited stage SCLC.
4. More experience with 3D-conformal radiotherapy, so patients with large tumors or poor pulmonary function are now offered this treatment.

Therefore the question is, have these changes resulted in an improvement in treatment and survival of lung cancer patients in South-East Scotland? This study was conducted to compare the original 1995 cohort with a group of patients diagnosed in 2002 to assess the impact of these changes on treatment and the median, 1- and 2-year survival.

METHODS AND MATERIALS

SCAN covers a population of 1.4 million in the 4 Scottish healthboard regions of Lothian, Borders, Fife, and Dumfries & Galloway. All radiotherapy is delivered at the Edinburgh Cancer Centre (ECC), which in 1995 had four, and in 2002, five linear accelerators. The majority of chemotherapy is delivered under the supervision of an oncologist, but in 2002 respiratory physicians still administered some chemotherapy. Lung cancer surgery is performed in the Royal Infirmary in Edinburgh, but patients living in Dumfries and Galloway usually have their surgery performed in Glasgow. Therefore, for this study only patients living in Lothian, Borders and Fife were included (population 1.2 million).

Data Sources

Integral to the development of the cancer networks has been the introduction of prospective audit. Cases are identified through the multidisciplinary team meetings, pathology reports, the ECC database, and the Scottish Cancer Registry. Data on patient characteristics including date of birth, sex, address, and performance status are collected. Tumor details are recorded, including how the diagnosis was made, staging investigations, pathologic type, and stage. Staging is recorded where possible according to the 1997 UICC TNM system. However, in the 1995 audit only "local," "regional," or "metastatic" stages were recorded so this was also noted for the 2002 patients.

Since 1995, the allocation of deprivation by postcode across Scotland has altered as some areas have become more affluent and others less so. Consequently, it is recommended that the Carstairs index based on the 2001 census is used in longitudinal studies.[7] Therefore, both the 1995 and 2002 cohorts were linked to the 2001 Carstairs Index.

Since 1974, the ECC has had a computerized database that includes data on all referred patients and includes details of all radiotherapy and chemotherapy treatments delivered under the supervision of the oncologists and tracks each patient's survival until death.

Firstly, patients residing in Lothian, Borders and Fife healthboard areas diagnosed with lung cancer in 2002 were identified from the SCAN and the ECC databases. Then pharmacy records from all the hospitals were checked to ensure all chemotherapy episodes had been identified. The hard-copy records of all thoracic operations were hand-searched and details of all lung cancer resections recorded.

Once a final list of patients managed under the care of the SCAN lung cancer team had been prepared, the database was then given to the Scottish Cancer Registry to identify any missing cases. Details of the patients who had not been identified by the audit, but had died were supplied to the research staff to check the medical records, but for those still alive only name, date of birth and contact details of their general practitioner (GP) were supplied. A condition of the ethical approval for this study was that these patients were required to give consent before the release of more detailed information.

The medical records of the additional cases were scrutinized to assess if they were eligible for entry into the audit and patient, tumor and management details recorded. For those patients whose hospital medical records could not be located, additional letters were sent to their GP to ask for further details.

The details of all cancer therapies delivered within 6 months of diagnosis were recorded. An exception was made for consolidation radiotherapy after chemotherapy in limited stage SCLC as this is part of the "initial treatment package," but can commence during the seventh month after diagnosis.

Treatment intent was defined as potentially curative therapy (PCT) if the patient had undergone either surgery, radical radiotherapy with a dose of $\geq$50 Gy, or for limited stage small-cell lung cancer chemo-radiation with thoracic radiotherapy with a dose of $\geq$30 Gy. These definitions were identical to those used in the 1995 audit.

To obtain up-to-date survival, the records of the General Register Office of Scotland were searched for notification of any patient deaths.

Once the database for 2002 patients was finalized, comparison was then made with the patients in the 1995 audit from Lothian, Borders and Fife. The details on the methods of data collection of the 1995 audit are set out elsewhere.[6] The 1995 audit excluded patients with a death certificate only diagnosis and those whose medical records could not be located.

The Multi-Centre Ethics Research Committee for Scotland granted ethical approval for this study.

Analysis

Patient, tumor, and management characteristics were analyzed using descriptive statistics and compared using either χ^2 for categorical or analysis of variance for continuous variables. Factors affecting the probability of use of treatment were examined using logistic regression models. Survival from time of diagnosis (pathologic confirmation or if not obtained, radiologic diagnosis) till death or last follow-up was estimated using the Kaplan Meier method and compared using log-rank tests and Cox's regression models.

RESULTS

In 2002, a total of 878 patients were identified by the SCAN audit and the Scottish Cancer Registry identified an additional possible 149 cases of which 106 were verified after location of their medical records. For the remaining 43 cases identified by the Cancer Registry, neither the hospital nor GP medical records could be located (unverified cases). Only two

of the unverified patients had not been under the care of a member of SCAN lung cancer team and were still alive. Neither patient could be contacted for permission to access their records so they were excluded. Therefore a total 984 verified cases and 43 unverified cases were identified.

Of the 3833 patients in the 1995 Scottish lung cancer audit, 927 were from Lothian, Borders or Fife. The proportion of cases in the Scottish Cancer Registry from the three health boards that were included the audit was much higher in the 2002 (94%) than in 1995 (86%).

Patient and Tumor Characteristics

In the 2002 cohort, there were no significant differences in the patient characteristics of the verified and unverified patients. Only 11 (26%) of the unverified cases had pathologic confirmation (recorded in cancer registry) compared with 716 (73%) the verified cases. Of the other verified cases, eight were confirmed at postmortem and 260 were diagnosed on radiology alone. In 86 (33%) of the radiologic-only diagnosis cases a biopsy had been performed, but was nondiagnostic. Thirteen cases were either confirmed at autopsy or died on the day they were diagnosed (3 SCLC, 8 NSCLC, and 2 radiologic), and as these patients would have been unable to receive any treatment they have been excluded from the analysis of management.

To investigate the impact of the improved case ascertainment, the Scottish Cancer Registry also provided data on the eligible cases from the 1995 audit that had been excluded because the medical records could not be located. There were 67 patients, of whom 39 were male and the median age was 75 (range, 34–92), over half this group (58%) died on the day they were diagnosed. There were no differences between the sex or age distribution of the 67 patients excluded from 1995 and the 56 excluded from the 2002 cohort.

The patient and tumor characteristics of the remaining 971 patients diagnosed in 2002 and of the 927 patients diagnosed in 1995 are shown in Table 1. Performance status was not collected in the 1995 audit.

A significantly higher proportion of patients underwent a staging CT scan in 2002 (85% versus 46% χ^2 $p < 0.001$). This may explain the apparently lower proportion of patients diagnosed with localized disease in 2002 (14% versus 25%) and higher proportion of patients with metastatic disease (42% versus 30%).

The median follow-up of the patients diagnosed in 2002 who were still alive was 40 months (range, 0.3–55).

TABLE 1. Patient and Tumor Characteristics in 1995 and 2002 Cohorts

	1995 (n = 927)	2002 (n = 984)	p
Sex, male	538 (58%)	537 (55%)	0.25
Age			
<60	135 (15%)	131 (14%)	0.002[a]
60–69	298 (32%)	246 (25%)	
70–79	359 (39%)	411 (42%)	
80+	135 (15%)	183 (19%)	
PFS			
0–1	—	396 (41%)	—
2		221 (22%)	
3–4		235 (24%)	
Unknown		132 (13%)	
Carstairs			
1	131 (14%)	149 (15%)	0.13
2	155 (17%)	175 (18%)	
3	240 (26%)	217 (22%)	
4	258 (28%)	316 (33%)	
5	120 (13%)[b]	114 (12%)	
Lothian	682 (74%)	605 (62%)	<0.001
Borders	53 (6%)	89 (9%)	
Fife	192 (21%)	277 (29%)	
Pathology			
NSCLC	543 (59%)	572 (59%)	0.055
SCLC	166 (18%)	141 (15%)	
No pathology	216 (23%)	258 (27%)	
Localized	229 (25%)	132 (14%)	<0.001
Regional	314 (34%)	339 (35%)	
Metastatic	275 (30%)	411 (42%)	
Unknown	109 (12%)	89 (9%)	
CT scan performed	430 (46%)	822 (85%)	<0.001

[a] ANOVA $p < 0.001$.
[b] For 23 data missing.
PFS, performance status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Management

No record could be found of any of the unverified cases from 2002 receiving any treatment for their lung cancer. On review of the medical records of the 106 patients identified only by the Cancer Registry none were felt to have been suitable for PCT. This group constituted mainly patients admitted under the care of Medicine for the Elderly and who died within a few days of entering hospital.

Details of the treatment delivered in 1995 and 2002 are shown in Table 2 . The overall proportion of patients receiving treatment did not increase in the 7 years; in 1995 63% received some form of treatment compared with 62% in 2002. Nevertheless, the proportion of patients treated with curative intent increased from 14% to 24% (χ^2 $p < 0.001$), primarily because of a trebling of the number of people treated with potentially curative radiotherapy (5% versus 15% χ^2 $p < 0.001$) The proportion of patients treated with radiotherapy overall did not change (45% versus 43%), however, those treated were more likely to have received a potentially curative dose.

Disappointingly there was no increase in the proportion under-going surgery for their lung cancer (10.2% versus 10.5% of all cases and 17.6% versus 16.8% NSCLC).

The number of patients receiving chemotherapy increased, mainly because of doubling of the use of chemotherapy in NSCLC (7% versus 18% χ^2 $p < 0.001$). The proportion of SCLC patients receiving chemotherapy did not change, and was 65% in 1995, and 68% in 2002 (χ^2 $p = 0.7$).

To investigate further, the factors that affected the use of "any treatment" and "PCT" a logistic regression analysis was performed (Table 3). The adjusted odds of receiving any treatment in 2002 was 1.3 (1.1–1.7) compared with 1995, and

TABLE 2. Management for Each Pathological Type in 1995 and 2002

	1995	2002
NSCLC		
Surgery only	**82 (15%)**	**78 (14%)**
Surgery and post-operative radiotherapy	**7 (1%)**	**19 (3%)**
Surgery and chemotherapy	**1 (0.2%)**	**2 (0.3)**
Surgery and palliative radiotherapy	**2 (0.4%)**	**2 (0.3%)**
Radical radiotherapy	**18 (3.3%)**	**50 (8.7%)**
Radical radiotherapy and chemotherapy	**1 (0.2%)**	**27 (4.7%)**
Palliative radiotherapy	*219 (40.5%)*	*174 (30.4%)*
Palliative radiotherapy and chemotherapy	*20 (4%)*	*32 (5.6%)*
Chemotherapy	*17 (3%)*	*39 (6.8%)*
None	176 (32.4%)	149 (26%)
SCLC		
Surgery and chemotherapy +/−RT	**1 (0.5%)**	**1 (0.5%)**
Chemotherapy and adjuvant radiotherapy	**12 (7%)**	**26 (18%)**
Palliative radiotherapy	*17 (10%)*	*10 (7%)*
Palliative radiotherapy and chemotherapy	*19 (11.5%)*	*17 (12%)*
Chemotherapy	*78 (46%)*	*52 (37%)*
None	39 (23%)	35 (25%)
No pathology		
Radical radiotherapy	**5 (2%)**	**24 (9%)**
Palliative radiotherapy	*79 (38%)*	*52 (20%)*
None	130 (60%)	182 (71%)

Bold, potentially curative treatment; Italics, palliative; %, percentage of pathological group.

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; RT, radiotherapy.

6.0 (4.3–8.4) for PCT. Older patients, those with more advanced disease and patients from Fife were less likely to receive both "any treatment" and "PCT." The lower rates in Fife were primarily due to fewer patients having radiotherapy, particularly with radical intent (in 2002 radical RT: 18% Lothian, 21% Borders, 8% Fife χ^2 $p = 0.001$).

Survival

The median overall survival for lung cancer patients in South-East Scotland increased from 4.1 month to 5.2 months in the 7 years from 1995 to 2002, and the overall survival at 2 years increased from 11% to 15%, and at 3 years from 8.0% to 11.5% (log rank $p = 0.004$) (Table 4 and Figure 1). For those patients who had pathologic confirmation (comparable to SEER data[8]) the median survival was 5.4 (4.5–6.2) months in 1995 and 5.9 (5.1–6.7) months in 2002, with 14% and 17.5% alive at 2-years and 10% and 12.5% alive at 3 years, in 1995 and 2002, respectively (log rank $p = 0.043$).

For the whole population cohort of 994 patients (927 + 67 excluded) diagnosed in 1995 and 1027 (971 + 56 excluded) patients from 2002, the median survival in 1995 was 3.6 (3.1–4.1) months and 4.8 (4.2–5.3) months in 2002, with 11% and 14% alive at 2 years and 8% and 10% at 3 years, respectively (log rank $p = 0.001$).

Reasons for the Improvement in Survival

To explore whether the improvement in survival observed was simply due to changes in patient and tumor characteristics, rather than the impact of increased use of treatment, a Cox's regression model analysis was performed. This demonstrated that even when the differences in age and stage were taken into account, patients diagnosed in 2002 had an adjusted hazard of death of 0.7 (0.6–0.8) compared with patients diagnosed in 1995. Localized disease, younger age, and pathologic confirmation were the only other factors associated with a reduced hazard of death.

When the model was repeated with the addition of the variable "treatment intent" (PCT versus palliative versus none) the hazard of death was still lower in 2002 compared with 1995 (hazard ratio 0.8; range, 0.7–0.9) suggesting that it was not just the increased use of PCT that was responsible for the improved outcome.

There was no change in the overall survival after surgery (2-year overall survival 77% versus 81%, 3-year 58% versus 54%, in 1995 and 2002 respectively, log rank $p = 0.94$), radical radiotherapy (2-year overall survival 25% versus 32% and 3-year 17% versus 25% log rank $p = 0.80$) chemoradiation for limited stage SCLC (2-year overall survival 50% versus 34% 3-year 25% versus 23% log rank $p = 0.80$), or palliative chemotherapy (1-year overall survival 25% versus 24% log rank $p = 0.50$). The latter three are reassuring because despite more patients receiving these treatments, a similar proportion benefited.

There was a slight decline in the median survival of patients undergoing palliative radiotherapy (5.2 to 4.4 months log rank $p = 0.009$), probably reflecting changes in patient selection. In 2002, palliative radiotherapy was delivered to patients unsuitable for either radical radiotherapy or palliative chemotherapy.

Relative Survival

An alternative explanation for the observed improvement in survival is the trend for increasing life expectancy in Scotland. Therefore to exclude this as a reason, the relative survival was calculated which estimates expected survival from nationwide population life tables stratified by age, sex, and calendar time. Relative survival estimates were produced using the methodology described by Dickman et al.[9] The standard error of the cumulative relative survivals were calculated using the Ederer method.[10]

This analysis demonstrated that there were significantly more patients alive at 12 months after diagnosis with a relative survival of 30.6% in 2002 compared with 24.7% in 1995 ($p < 0.005$). The difference in relative survival at 24 months after diagnosis was also found to be significant (16.4% versus 12.4% $p = 0.02$). The relative survival at 3 years was not statistically significantly different, but the numbers of patients included in the analysis at this time point was small (106 and 143) (Table 5).

DISCUSSION

Over recent years, population-based cancer survival for a number of tumors, such as colorectal and breast cancers have shown a gratifying improvement.[11] Unfortunately, despite improvements in surgery, radiotherapy and chemotherapy population-based survival for lung cancer patients has changed very little.[2,3,12]

TABLE 3. Factors Affecting Use of 'Any Treatment' and 'Potentially' Curative Treatment (PCT)

	Any Treatment	χ^2 *p* Value	Unadjusted Odds Any Treatment	Adjusted Odds of Any Treatment	PCT	χ^2 *p* Value	Unadjusted Odds of PCT	Adjusted Odds of PCT
Male	681 (63%)	0.42	1	1	207 (19%)	0.72	1	1
Female	506 (62%)		0.9 (0.8–1.1)	0.9 (0.7–1.1)	153 (19%)		1.0 (0.8–1.2)	0.9 (0.7–1.2)
<60	223 (84%)	<0.001	1	1	85 (32%)	<0.001	1	1
60–69	406 (75%)		0.6 (0.4–0.8)	0.7 (0.4–0.99)	137 (25%)		0.7 (0.5–0.99)	0.6 (0.4–0.9)
70–79	457 (59%		0.3 (0.2–0.4)	0.4 (0.2–0.5)	119 (16%)		0.4 (0.3–0.5)	0.3 (0.2–0.4)
80+	101 (32%)		0.1 (0.06–0.13)	0.1 (0.08–0.2)	19 (6%)		0.1 (0.08–0.2)	0.1 (0.03–0.12)
Carstairs								
1	176 (63%)	0.76	1	1	66 (24%)	0.33	1	1
2	214 (65%)		1.0 (0.8–1.5)	1.0 (0.7–1.5)	60 (18%)		0.7 (90.5–1.1)	0.7 (0.4–1.1)
3	287 (63%)		1.0 (0.7–1.4)	0.9 (0.6–1.3)	84 (18%)		0.7 (0.5–1.1)	0.7 (0.4–1.1)
4	347 (61%)		0.9 (0.7–1.2)	0.9 (0.6–1.3)	103 (18%)		0.4 (0.5–1.0)	0.6 (0.4–1.04)
5	148 (63%)		1.0 (0.7–1.5)	1.0 (0.6–1.5)	47 (20%)		0.8 (0.5–1.2)	0.6 (0.3–1.04)
Lothian	835 (65%	<0.001	1	1	272 (21%)	0.001	1	1
Borders	95 (67%)		1.1 (0.8–1.6)	1.2 (0.8–2.0)	25 (18%)		0.8 (0.5–1.3)	0.6 (0.3–1.1)
Fife	257 (55%)		0.7 (0.5–0.8)	0.7 (0.5–0.9)	63 (13%)		0.6 (0.4–0.8)	0.5 (0.3–0.7)
NSCLC	790 (71%)	<0.001	1	1	289 (26%)	<0.001	1	1
SCLC	235 (76%)		1.3 (1.0–1.7)	1.8 (1.3–2.5)	42 (14%)		0.5 (0.3–0.6)	1.3 (0.8–2.1)
No path	162 (34%)		0.2 (0.1–0.3)	0.3 (0.2–0.4)	29 (6%)		0.2 (0.1–0.3)	0.2 (0.1–0.4)
Localized	272 (75%)	<0.001	1	1	165 (45%)	<0.001	1	1
Regional	485 (74%)		0.9 (0.7–1.3)	0.7 (0.5–0.99)	188 (29%)		0.5 (0.4–0.6)	0.2 (0.16–0.3)
Metastatic	397 (58%)		0.4 (0.3–0.6)	0.3 (0.2–0.5)	8 (1%)		0.01 (0–0.03)	0.004 (0–0.009)
Unknown	33 (17%)		0.07 (0.–0.1)	0.1 (0.05–0.1)	0		—	—
1995	582 (63%)	0.83	1	1	131 (14%)	<0.001	1	1
2002	605 (62%)		1.0 (0.8–1.2)	1.3 (1.06–1.7)	229 (24%)		1.9 (1.5–2.4)	6.0 (4.3–8.5)

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

TABLE 4. Overall Survival in South-East Scotland 1995 vs. 2002

	Median	1 yr	2 yr	3 yr	Log Rank
1995 (n = 927)	4.1 (3.5–4.6)	23.4% (20.7–26.1)	11.4% (9.3–13.5)	8.3 (6.5–10.0)	0.004
2002 (n = 971)	5.2 (4.5–5.8)	29.1% (26.3–31.9)	14.8% (12.7–17.2)	10.5 (8.6–12.7)	

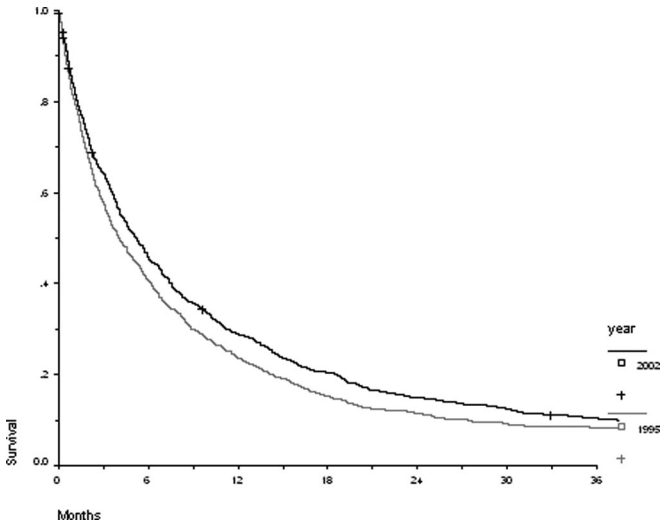

FIGURE 1. Comparison of lung cancer survival in South-East Scotland 1995 versus 2002.

Lung cancer survival in Scotland, and the United Kingdom as a whole,[2] is lower than that reported in many European countries, Australia, and North America.[3,13–21] The reasons for this inferior outcome are complex, but relate to differences in data collection and reporting, patient and tumor characteristics, and treatment.[22]

The methodology used in this study, including hospital and community diagnosed patients, and both pathologically confirmed and radiology-only diagnosed cases, ensures that the management and survival described reflects the true population-based figures. Many studies are restricted to only a subset of patients or do not include nonpathologically confirmed cases.[8] As shown in this study, exclusion of this latter group can have a major impact on outcome (median survival of 4.6 months when patients with a radiology-only diagnosis are included versus 5.6 months when these cases are excluded). The two cohorts were recorded and analyzed in a similar manner to ensure, as closely as possible, a valid comparison. The higher case ascertainment in the later cohort would, if anything, have resulted in the identification of older

TABLE 5. Relative Survival in South-East Scotland 1995 vs. 2002

	1 yr Since Diagnosis		2 yr Since Diagnosis		3 yr Since Diagnosis	
1995	$n = 927$	24.7% (21.8–27.6)	$n = 218$	12.4 (10.3–14.8)	$n = 106$	9.3 (7.5–11.4)
2002	$n = 971$	30.6% (27.7–33.7)	$n = 278$	16.4 (14.0–19.0)	$n = 143$	12.0 (9.9–14.3)
2002 vs. 1995	$p < 0.005$		$p = 0.020$		$p = 0.077$	

patients, with more advanced disease who were less likely to receive treatment.

Over the 7-year period, the median age of the population increased from 70 to 72 years. This trend will continue as the Scottish birth cohorts with the highest lung cancer risk become older.[23] This will present an increasing challenge to lung cancer specialists as the majority of cancer therapies, but particularly surgery,[24–26] are more difficult to deliver to elderly patients. This aging trend is seen in most other Western countries with most recent series reporting median (or mean) ages of 65 to 70 years.[14,15,19,21,27] The other patient characteristics, such as sex and deprivation did not change, though more patients in the later cohort came from Fife. As the Scottish Cancer Registry had not recorded a similar change this was probably a consequence of improved case-ascertainment, rather than changes in incidence in Fife.

There was no statistical difference in the pathologic types of lung cancer, but there was an apparent increase in the proportion of patients presenting with metastatic disease. It seems unlikely that this is genuine, but is more likely to reflect (i) the higher case ascertainment, (ii) greater use of CT scanning, and (iii) technical improvements in CT scanning and more experienced radiologists resulting in higher detection of metastatic deposits. Positron emission tomography scans were not routinely available in South-East Scotland in 2002.

The proportion of 42% of patients in 2002 presenting with distant disease is similar to that seen in many population-based series, though 14% of cases with localized disease is a little lower. Most recent series report around 20% of patients with localized disease.[14–19,21,28] The lower proportion of patients with early stage cancers will inevitably impact on long-term survival figures.

Treatment

The crude rate of use of treatment did not increase over time, with 38% of lung cancer patients not receiving any form of therapy. "No-treatment" rates vary greatly around the world; from 85% of patients in some areas of South-East England[29] to 28% in New South Wales.[21] The optimal use of treatment in any one population will vary depending on the patients' and tumors' suitability for treatment. A population with a fit population presenting with more localized disease will, in general, be more suitable for treatment. Scotland has one of the highest rates of cardiovascular disease in the world,[30] which makes surgery and platinum-based chemotherapy more hazardous.

Although the use of treatment overall did not increase, the use of "PCT" nearly doubled. This was not because of an increase in surgery, which remained static at just over 10% of the population, however, the use of potentially curative radiotherapy trebled. The resection rate is much lower than most international series which report rates of 19% to 26%,[14,18,19,21,28] but similar to other UK and Irish series.[27,29,31] The lack improved resection rates is likely to be because of the low proportion of patients presenting with early stage disease and high prevalence of comorbid disease.

The population-based use of radical radiotherapy was 15% is high, but there are few data to compare as few other population-based series report radiotherapy intent. In a companion study, a cohort of patients diagnosed in British Columbia in 1995 of 2073 patients, 3.7% received radical radiotherapy (unpublished data Erridge et al.). In a Dutch series of 807 patients with NSCLC 15%), patients with Stage I–II and 30% patients with Stage IIIA disease received radical radiotherapy. This compares with 30% and 22%, respectively, in South-East Scotland in 2002.

Although there was an increase in use of radical radiotherapy across the region, there were significant variations between the three health boards. The causes of this are unclear as the patients are managed according to the same protocols and the rate of pathologic confirmation and CT scanning was similar between the health boards suggesting the variation was not was not therapeutic nihilism. The most likely explanation is variation in levels of comorbidity, but a prospective study on the rationale behind management choices is required to understand the variation in management across the region more fully.

While the use of potentially curative radiotherapy increased, the use of radiotherapy in general did not. The population-based rate of radiotherapy in the first 6 months after diagnosis remained at around 45%. This rate is similar to other studies that include nonpathologically confirmed cases,[19,27,31–33] but a little lower than in SEER series.[14,17,34] Models estimating the optimal use of radiotherapy in Canada[35] and Australia[36] suggested between 61% and 76% of lung cancer patients should receive this treatment during their illness. A benchmarking study in Canada suggested that around 41% might be more appropriate rate.[34] Over recent years, the use of palliative radiotherapy actually reduced in South-East Scotland (41% versus 29%). This is probably because of increased use of radical radiotherapy and also palliative chemotherapy that confers a survival benefit not seen with low-dose palliative radiotherapy. A similar trend has also been seen in the Netherlands[33] and the United States.[37]

The use of chemotherapy for NSCLC increased from 7% to 18%. This follows the publication of evidence on the survival benefit, without cost to quality of life, in patients with metastatic disease[38] and in combination with radical radiotherapy.[39] The data on the role of adjuvant postoperative chemotherapy was not available in 2002 so this was not in routine use at this time. The increase in use of chemotherapy

in metastatic disease will have a moderate impact on median and 1-year survival, but little impact on 2-year survival.

The use of chemotherapy in NSCLC in 2002 is similar to that seen in most series from the late 1990s,[21,27,32] and one English series, which includes patients from 2002[40], though it is difficult to establish the use in United States as SEER does not collect data on chemotherapy. Consequently, these data are only available for the United States from Medicare for patients over 65 years of age.[41]

The use of chemotherapy for SCLC in South-East Scotland remained relatively stable (65% versus 68%), but a little lower than in other countries where the rates of chemotherapy use range from 73% to 92% of patients with SCLC,[21,32,42] however, the rate in South-East Scotland was higher than in South-East England (50%) in the same period.[40] There was an increase in the proportion of SCLC patients receiving chemo-radiation from 7% to 18%. This will increase the number of long-term survivors slightly, but limited stage SCLC patients constitute only around 6% of the whole lung cancer population. Consequently, a survival rate of 40% at 2 years and 20% at 5 years[43] translates to around a 2.4% and 1.2% increase in population-based survival, respectively.

Survival

The overall survival and relative survival of lung cancer patients in South-East Scotland improved over the period from 1995 to 2002. Although the median survival only increased by 1 month, the absolute increase at 2 years was 4.8%, which represents nearly a 50% improvement. There are very few reports of improved population-based survival for lung cancer patients. Gadgeel et al.[17] reported improved survival in Detroit over the period 1973–1993 for white, but not black patients and Lebitasy et al. reported improved survival for patients with SCLC over the period 1981–1994, but no improvement was seen in patients with NSCLC from the same region.[42,44] A recent analysis of the outcome of lung cancer patients in Sweden over the last 40 years demonstrated an improvement in the 1-year relative survival for patients with adenocarcinoma and squamous cell tumors, but no improvement was seen after 5 years.[45] Several other studies have been unable to identify an improvement.[2,3,12]

The changes in patient and tumor characteristics would, if anything, have a detrimental impact on outcome. Increased lead-time due to earlier diagnosis could be contributory, but this is unlikely because the outcome after specific treatments was unchanged.

The increased use of treatment, particularly the increased use of radical radiotherapy, is likely to be contributory to the improved survival. Over the period 1995 to 2002, new radiotherapy techniques and greater experience of the oncologists enabled patients with bulky tumors or poor pulmonary function to be offered this treatment. As the number of patients receiving treatment, particularly radiotherapy, has not increased it appears the increased use of radical radiotherapy is primarily because of a change in approach of the oncologists rather than an effect of the wider changes in the structure of the lung cancer service. The role of the introduction of multidisciplinary meetings in the change of management is difficult to establish; one would have expected the proportion of patients treated to increase had this had a major impact. The development of team-based management of patients by the lung cancer oncologists may have provided the supportive and educational environment to enable the change in radiotherapy intent and increased use of chemotherapy.

Nevertheless, when the variable "treatment intent" was included in the Cox's proportional hazards model, the hazard of death in 2002 remained significantly reduced suggesting that other uncharacterized factors not collected in this study, such as comorbidity and patient choice might also be important.

CONCLUSIONS

There has been a demonstrable improvement in the duration of survival of lung cancer patients in South-East Scotland. This appears to be due at least in part to more patients receiving radical radiotherapy, and to a lesser extent chemo-radiation for limited stage SCLC and palliative chemotherapy for NSCLC.

Although the rates of treatment and survival have increased, there are still variations in treatment within the region. The reasons for this are as yet unclear, however, there is a view that this maybe related to regional variations in levels of co morbid disease. A prospective study on the rationale behind management choices is required to understand the variation in management across the region.

ACKNOWLEDGMENTS

We thank Jamie Megaw, Claire Egan and the other members of the South-East Scotland Cancer Network audit team for their assistance in collecting the 2002 data, Gill Kerr, Statistician Edinburgh Cancer Centre for providing the treatment data, Jillian Campbell, ISD NHS Scotland for the cancer registry data and Anna Gregor, Lead Cancer Clinical South-East Scotland Cancer Network and other members of the Scottish Lung Cancer Trials Group who instigated the original 1995 Scottish audit.

REFERENCES

1. Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. *Lancet Oncol* 2007;8:773–783.
2. Coleman MP, Rachet B, Woods LM, et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *B J Cancer* 2004;90:1367–1373.
3. Talback M, Stenbeck M, Rosen M, et al. Cancer survival in Sweden 1960–1998–developments across four decades. *Acta Oncologica* 2003; 42:637–659.
4. Erridge SC, Thomson CS, Davidson J, et al. Factors influencing the use of thoracic radiotherapy in lung cancer-an analysis of the 1995 Scottish lung cancer audit. *Clin Oncol (R Coll Radiol)* 2002;14:219–227.
5. Fergusson RJ, Thomson CS, Brewster D, et al. Lung cancer: the importance of seeing a respiratory physician. *Eur Respir J* 2003;21:606–610.
6. Gregor A, Thomson CS, Brewster DH, et al. Management and survival of patients with lung cancer in Scotland diagnosed in 1995: results of a national population based study. *Thorax* 2001;56:212–217.
7. Information-Statistics-Division. Available at: www.isdscotland.org. Accessed March 31, 2008.
8. Butler CA, Currie GP, Anderson WJ. Do differences in data reporting contribute to variation in lung cancer survival? *Journal of the National Cancer Institute* 2005;97:1385.
9. Dickman PW, Coviello E, Hills M. Estimating and modeling relative survival. http://www.pauldickman.com/survival/strs.pdf.

10. Ederer F, Axtell L, Cutler S. The Relative Survival Rate: A Statistical Methodology. *National Cancer Institute Monograph* 1961;6:101–121.
11. Coleman M, Gatta G, Verdecchia A, et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Ann Oncol* 2003;14(suppl 5):128–149.
12. Laskin JJ, Erridge SC, Coldman AJ, et al. Population-based outcomes for small cell lung cancer: impact of standard management policies in British Columbia [see comment]. *Lung Cancer* 2004;43:7–16.
13. Bossard N, Velten M, Remontet L, et al. Survival of cancer patients in France: A population-based study from The Association of the French Cancer Registries (FRANCIM). *Eur J Cancer* 2006;43:149–160.
14. Fu JB, Kau TY, Severson RK, et al. Lung cancer in women: analysis of the SEER database. *Chest* 2005;127:768–777.
15. Campling BG, Hwang WT, Zhang J, et al. A population-based study of lung carcinoma in Pennsylvania: comparison of Veterans Administration and civilian populations. *Cancer* 2005;104:833–840.
16. Demeter SJ, Chmielowiec C, Logus W, et al. The descriptive epidemiology of primary lung cancer in an Alberta cohort with a multivariate analysis of survival to two years. *Canadian Respiratory J* 2003;10:435–441.
17. Gadgeel SM, Severson RK, Kau Y, et al. Impact of race in lung cancer: analysis of temporal trends from a SEER database. *Chest* 2001;120:55–63.
18. McDavid K, Tucker TC, Sloggett A, et al. Cancer survival in Kentucky and health insurance coverage. *Arch Intern Med* 2003;163:2135–2144.
19. Richardson GE, Thursfield VJ, Giles GG. Reported management of lung cancer in Victoria in 1993: comparison with best practice. Anti-Cancer Council of Victoria Lung Cancer Study Group. [see comment]. *Med J Australia* 2000;172:321–324.
20. Sant M, Aareleid T, Berrino F, et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94–results and commentary. *Ann Oncol* 2003; 14(suppl 5):v61–v118.
21. Vinod SK, Hui AC, Esmaili N, et al. Comparison of patterns of care in lung cancer in three area health services in New South Wales, Australia. *Intern Med J* 2004;34:677–683.
22. Erridge S, Moller H, Price A, et al. International comparisons of survival from lung cancer: pitfalls and warnings. *Nat Clin Pract Oncol* 2007; in press.
23. Harkness EF, Brewster DH, Kerr KM, et al. Changing trends in incidence of lung cancer by histologic type in Scotland. *Int J Cancer* 2002;102:179–183.
24. Berrisford R, Brunelli A, Rocco G, et al. The European Thoracic Surgery Database project: modelling the risk of in-hospital death following lung resection. *Eur J Cardiothorac Surg* 2005;28:306–311.
25. Freixinet J, Julia-Serda G, Rodriguez P, et al. Hospital volume: operative morbidity, mortality and survival in thoracotomy for lung cancer. A Spanish multicenter study of 2994 cases. *Eur J Cardiothorac Surg* 2006;21:20–25.
26. Strand T, Rostad H, Moller B, et al. Survival after resection for primary lung cancer. A population-based material of 3211 resected patients. *Thorax* 2006.
27. Mahmud SM, Reilly M, Comber H. Patterns of initial management of lung cancer in the Republic of Ireland: a population-based observational study. *Lung Cancer* 2003;41:57–64.
28. Makitaro R, Paakko P, Huhti E, et al. Prospective population-based study on the survival of patients with lung cancer. *Eur Respir J* 2002;19:1087–1092.
29. Jack RH, Gulliford MC, Ferguson J, et al. Geographical inequalities in lung cancer management and survival in South East England: evidence of variation in access to oncology services? [erratum appears in *Br J Cancer* 2004 Nov 15;91(10):1852.] *Br J Cancer* 2003;88:1025–1031.
30. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from WHO MONICA project. *Lancet* 1999;353:1547–1557.
31. Cartman ML, Hatfield AC, Muers MF, et al. Lung cancer: district active treatment rates affect survival. *J Epidemiol Community Health* 2002;56: 424–429.
32. de Rijke JM, Schouten LJ, ten Velde GP, et al. Influence of age, comorbidity and performance status on the choice of treatment for patients with NSCLC; results of a population-based study. *Lung Cancer* 2004;46:233–245.
33. Vulto AJ, Louwman MW, Rodrigus P, et al. Referral rates and trends in radiotherapy as part of primary treatment in cancer in South Netherlands, 1988–2002. *Radiother Oncol* 2006;78:131–137.
34. Barbera L, Zhang-Salomons J, Huang J, et al. Defining the need for radiotherapy for lung cancer in the general population: a benchmarking approach. *Medical Care* 2003;41:1074–1085.
35. Tyldesley S, Boyd C, Schulze K, et al. Estimating the need for radiotherapy for lung cancer: an evidence-based, epidemiologic approach. *Int J Radiat Oncol Biol Phys* 2001;49:973–985.
36. Delaney G, Barton M, Jacob S, et al. A model for decision making for the use of radiotherapy in lung cancer. *Lancet Oncol* 2003;4:120–128.
37. Hayman J, Abrahamse P, Lakhani I, et al. Use of palliative radiotherapy among patients with metastatic non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2007;69:1001–1007.
38. Cullen MH, Billingham LJ, Woodroffe CM, et al. Mitomycin, ifosfamide, and cisplatin in un-resectable non-small-cell lung cancer: effects on survival and quality of life. *J Clin Oncol* 1999;17:3188–3194.
39. Anonymous. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ* 1995;311:899–909.
40. Patel N, Adatia R, Mellemgaard A, et al. Variation in the use of chemotherapy in lung cancer. *Br J Cancer* 2007;96:86–90.
41. Earle CC, Neumann PJ, Gelber RD, et al. Impact of referral patterns on the use of chemotherapy for lung cancer. *J Clin Oncol* 2002;20:1786–1792.
42. Lebitasy M, Hedelin G, Purohit A, et al. Progress in the management and outcome of small-cell lung cancer in a French region from 1981 to 1994. *Br J Cancer* 2001;85:808–815.
43. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide [see comment]. *N Engl J Med* 1999;340:265–271.
44. Foegle J, Hedelin G, Lebitasy MP, et al. Non-small-cell lung cancer in a French department, (1982–1997): management and outcome. *B J Cancer* 2005;92:459–66.
45. Brooks D, Klint A, Dickman P, et al. Temporal trends in NSCLC survival in Sweden. *Br J Cancer* 2007;96:519–522.